THE FEMALE SEX HORMONES

HANS O. HATERIUS
The Ohio State University College of Medicine

I. THE OVARIAN CYCLE

In the short period of maturity preceding rupture the Graafian follicle increases rapidly in size, a process characterized by changes in the theca interna cells and by a loosening of the ovum in its enveloping granulosa. The ovum itself attains the stage of maturation. Since in most mammals this stage of follicular maturity occurs simultaneously with the pro-oestrous phase of the cycle, that is, the stage immediately prior to sexual receptivity, and since in most species the ripe follicle ruptures spontaneously with the ensuing oestrous phase, one may generalize to the extent of stating that oestrus and ovulation are essentially contemporary phenomena in animals displaying a well-defined oestrous cycle.

The ovum after its release is carried through the Fallopian tube and, in due course, arrives in the uterine cavity—the time required for this journey averaging about three days, according to Corner, "with singular unanimity regardless of species and the widely variant length of the tube." In the uterus, in the absence of impregnation, it rapidly degenerates. In the event of fertilization, which occurs in the tube or in the body cavity, the ovum, upon reaching the uterine cavity, becomes implanted in the prepared endometrial bed, the precise process of which varies according to species. Upon fertilization, we speak of the entire cycle of activity as the "reproductive cycle," in contrast to the term "sexual cycle," applied in the absence of pregnancy.

Following upon follicular rupture and extrusion of the ovum, the walls, composed in the intact stage of rows of granulosa cells, undergo a comparatively rapid change in structure; the granulosa cells, and in some species certainly, the theca interna as well, enlarge and become fat-laden, richly supplied with capillaries, forming ultimately a prominent compact body, the *corpus luteum*. In the event of impregnation, this grows large and persists functionally until nearly the end of gestation. In the absence of fertilization it persists for a variable period, according to species; in most forms at least long enough to allow the ovum, if fertilized, to become implanted.

The primary—and first known—function of the follicular apparatus is that of nourishing and discharging the ovum. A second function, the incretory one, was discovered much more recently, and is only now coming to be understood. The corpus luteum, so far as we know, is essentially incretory in function, its secretion being quite distinct from, and in certain respects perhaps antagonistic to, that of the Graafian follicle.

II. SEARCH FOR THE OVARIAN HORMONES

With the cyclic changes which occur in the ovary as a background, it now becomes necessary to anticipate somewhat, by listing the essential endocrine functions of the female gonad as these have been established. In general, these may be summarized as:

1. Control of onset of puberty; this includes development of primary and secondary sexual characters, and, to some degree perhaps, normal body growth.
2. Maintenance of the accessory organs of reproduction.
3. Preparation of accessory organs for mating. This includes as well the behaviour-pattern of the animal.
4. Preparation of the endometrium for implantation of the fertilized egg.
5. Maintenance of the endometrium for nourishment of the embryo.
6. Preparation of the genitalia for parturition.
7. Growth and preparation of the mammary glands for lactation. (Lactation, it should be noted, is not *initiated* by gonadal hormones; this specific and climactic duty is relegated to a pituitary factor).

With this list, then, of established functions, let us consider briefly the history of the arduous researches which placed these observations upon a firm experimental basis.

Our knowledge of female reproductive physiology began with the demonstration of Knauer (1896) that transplantation of ovaries in the experimental animal prevented the uterine atrophy which characteristically follows upon oophorectomy. His observation soon was confirmed and extended, particularly by Halban (1900) who, showed, in addition, that subcutaneous ovarian transplantation in the immature castrate female guinea pig resulted in attainment of normal puberty. In short, the ovarian functions include not only *maintenance* of the genital tract but its physiological *development* as well. Halban's

observations have been confirmed and amplified in numerous laboratories since that time.

On the basis of these discoveries, an internal secretion was postulated. Conceived of as a single substance, considerable speculation arose as to its source. Early attempts at testing the secretion by the injection of ovarian extracts were largely unsuccessful or, at best, unconvincing and, although this method of approach was instituted in 1900 it was not until 1912 that Adler was able to produce indications of sexual activity in spayed animals with administration of aqueous extracts.

Numerous experiments were carried out in ensuing years, but final identification of an ovarian hormone awaited the striking experiments of Allen and Doisy (1922 *et seq.*). Their work of qualitative and quantitative assay was tremendously facilitated by a test reaction which had been unavailable to earlier investigators, namely that afforded by the vaginal smear technique, by means of which the vaginal rhythm, discovered in 1917 by Stockard and Papanicolaou, could be followed. Prior to 1917, the effects of test material injections could be ascertained only by the costly and time-consuming process of sacrificing the experimental animals. Stockard and Papanicolaou, however, found that the cellular changes in the vaginal lumen, as detected by examination of vaginal lavage contents, were rhythmic in nature, the rhythm corresponding precisely to phases in the ovarian cycle. Since such changes disappeared upon castration, their reappearance upon the injection of suitable extracts could mean only that an active principle was being employed and, moreover, that its effect could be *measured*. Using fluid aspirated from sow's ovaries, Allen and Doisy soon were able to arrive as a quantitative assay, and developed the Rat Unit of the ovarian follicular hormone. The value of their work, and the stimulus it provided to research in reproductive physiology, was incalculable. An adequate method for assaying was provided, which included at the same time a method for estimating potency. This accurate and simple means of bio-assay resulted in many new and fundamental discoveries.

Then, Frank, with his collaborators, in 1925 demonstrated the same active principle in circulating and menstrual blood in the human being. Moreover, it was shown to be cyclic in quantity, the average intermenstrual peak running about one Mouse Unit per forty cubic centimeters of blood. Larger amounts were found in the blood of pregnant women. The principle, indeed,

came to be regarded as *the* "female sex hormone." Detailed chemical work was hampered severely, however, for several years by paucity of raw material. This impasse was dissipated three years later by Zondek. In connection with his epochal work on the gonadal relations of the anterior pituitary Zondek reported that urine of pregnancy contains tremendous amounts of ovarian oestrogenic hormone. This discovery proved extremely timely, in that it provided an abundant and cheap source of material, in aqueous medium and adaptable to chemical manipulation. In consequence, from 1928 onward progress has been amazingly rapid.

Chemists were quick to appreciate the practical importance of Zondek's findings, and chemical purification proved only a matter of time; only a year later Allen and Doisy and, independently, Butenandt, reported crystallization of the oestrogenic hormone, the product of which was named "theelin" by the former investigators.

Now, the discoveries of the 1920's led many to believe in a single ovarian hormone. Here was a substance which fulfilled a great many of the functions detailed above, and it seemed probable that upon proper testing it would satisfy as well the remainder of the rigid functional requirements. Doubts still persisted in some quarters, however, and this necessitates going back again some thirty-seven years to the turn of the century.

Reference has been made already to the corpus luteum. Now, this structure is present typically during pregnancy; its invariable association with the latter condition, indeed, led to many early speculations as to its possible functional significance.

Its coincidence with gestation had been noted, for example, by John Beard, in 1897, who, on purely theoretical grounds, postulated it to be essentially an "organ of pregnancy—that it served a necessary function during the course of gestation, probably in the maintenance of conditions essential to pregnancy. His reasoning was strictly of the arm-chair variety, but it is striking to reflect how closely he hit upon the truth. The German investigator, Born, (1900) speculated also, and in somewhat more detailed manner remarked upon the fact that in placental mammals, and in them only, a fully developed corpus luteum is always present and that it acquires its peak of development just when the embryo is attached to the uterus and the placenta is beginning to form. He observed also the decidual reaction on the part of the uterine mucosa, and suggested that these changes

were the result of an internal secretion of the corpus luteum—and *not* the result of stimulus provided by the ovum-mechanism as was popularly supposed at that time. In short, the corpus luteum, by virtue of an internal secretion, prepared the mucosa for reception and implantation of the fertilized egg. Born died in the midst of his speculations, and the burden of experimental proof fell to his student Fraenkel (1903).

Reasoning that if Born were correct in assuming that implantation and placentation depend upon the corpus luteum, Fraenkel came to the conclusion that, *ipso facto*, early removal of the ovaries should prevent these phenomena from occurring. Accordingly, he extirpated the ovaries or destroyed the corpora lutea in recently mated rabbits. He was able to prove the hypothesis; implantation of embryos was prevented and pregnancy met an untimely interruption.

Leo Loeb (1907) furnished additional proof, now classical, of the incretory function of the corpus luteum. Loeb showed that the endometrium of the guinea pig, sensitized by the corpus luteum hormone, develops the decidual, or maternal, growth reaction as the result of the irritating effect of the early embryo *in utero*. For example, glass beads were inserted in the uterus following upon sterile copulation, upon the day when implantation normally should have occurred. A tumour of decidual cells developed in response. Loeb's work constituted the first experimental proof that the secretion of the corpus luteum prepares the endometrium for decidual response. This work has been amply confirmed and constituted for a long time the classical test for corpus luteum extracts. On the basis of Fraenkel's and of Loeb's observations, indeed, it was long believed by many that the corpus luteum supplied *the* ovarian hormone, and that none other was concerned.

The foregoing observations led two French investigators, Bouin and Ancel in 1910 to study the uterine changes in the rabbit, prepared in such manner as to possess functional corpora lutea in the absence of pregnancy. They utilized the fact that rabbits ovulate only upon mating, and for mating employed sterile (vasectomized) males, with the result that ovulation and corpus luteum formation was obtained without the supervention of pregnancy. Under this circumstance the corpora lutea develop just as though pregnancy had ensued, and persist for an appreciable time (some two weeks in the rabbit) during which the uterus undergoes changes typical of those occurring during

gestation—in brief, a condition of *pseudo-pregnancy*. It was noted that the endometrium, the lining membrane of the uterus, underwent a characteristic proliferation, quite similar in detail to that typical of early pregnancy, and not unlike that displayed by the human endometrium late in the menstrual cycle. These proliferative changes attained a maximum in about eight days, after which retrogression set in, and the stage of rest was resumed in slightly more than three weeks. These changes never occurred in the absence of ovulation and corpus luteum formation.

The situation rested at this point until 1929, at a time when the so-called follicular hormone was attracting almost exclusive attention, when Corner, with a background of years of histological and experimental work on the physiology of reproduction, re-investigated the problem of the corpus luteum and settled the question of a possible internal secretion once and for all in a thorough-going series of experiments. To summarize these briefly, his observations may conveniently be condensed into three statements:

Ovaries were removed from rabbits 14–20 hours *post coitum*, at a time when the ova had been in the tubes 4–10 hours. In all cases there was complete failure on the part of the uterine mucosa to produce progestational changes such as those to be seen in intact females following upon mating. Embryos failed to survive. This observation confirmed Fraenkel and Ancel and Bouin.

Females were mated and, 18 hours later, were spayed, at which time small portions of the uterus were removed for examination. Injections then were given of a corpus luteum extract (obtained from the ovaries of pregnant sows). Upon the 6th day the animals were sacrificed, the embryos and uterus removed and examined histologically. In all respects both presented the same appearance as similar preparations from the intact 6-day pregnant animal.

Controls, carried out precisely as the foregoing, were given follicular hormone in place of the corpus luteum extract. As in the initial observations, none of the embryos lived, and the mucosa revealed no progestational changes.

As this very sketchy resumé shows, then, Corner's excellent work placed the proof of incretory function of the corpus luteum upon a firmly established basis. The active principle was named "progestin," and the observations made in the

Rochester laboratory soon were amply confirmed elsewhere. Corner and his student, Willard Allen, studied the various properties of their extract and continued its purification, a procedure which culminated in 1933 in the announcement of a crystalline product possessing all the known properties of the active principle. This was confirmed almost immediately in a number of laboratories (e. g. Fels and Slotta). Its structure was quickly established (Wintersteiner and Allen; Slotta *et alii*), and it was assigned the empirical formula $C_{21}H_{30}O_2$.

III. CHEMISTRY OF THE FEMALE SEX HORMONES

With the experimental proof established, and the purification achieved, let us next consider the progress attained in studies of the chemistry of these principles.

At the time the oestrogenic hormone was isolated and crystallized, Doisy gave it the empirical formula $C_{18}H_{22}O_2$ (theelin). Difficulty was anticipated, however, in clearing up its structural formula, and one would have been optimistic indeed at the time to have predicted that in the space of a few years this would be completely solved. We have here an instance, however, of how progress in a field apparently quite remote helped provide an extremely valuable key to the solution of the chemistry of gonadal principles. Fundamental researches by Windaus and Wieland culminated in 1928 by their demonstration of a close structural relationship between the bile acids and the sterols, in the course of which—and relevant to the subject at hand—they unravelled the chemistry of cholesterol. Capitalizing upon this work, Butenandt, in 1933, was able to show that structurally the sex hormones are related to this same group—a fact which had been suspected for some time. Moreover, pregnandiol $C_{21}H_{36}O_2$, a physiologically inert substance from pregnancy urine (Marrian, 1929; Butenandt 1929), separable from theelin and theelol, was converted by Butenandt into *progesterone*, the purified progestin. It is not inconceivable, furthermore, that pregnandiol, in turn might be formed in the body from cholesterol, and might be regarded as an intermediate stage in the formation of gonadal hormones from cholesterol (or bile acids). It should be noted incidentally that Ruzicka has reported conversion of cholesterol into male sex hormone.

Three oestrogenic principles have been obtained from female tissues: oestrone—$C_{18}H_{22}O_2$, oestriol—$C_{18}H_{24}O_3$, and oestradiol—$C_{18}H_{24}O_2$, the last a dihydroxy derivative of oestrone, or

dihydro-oestrone. In addition, the corpus luteum hormone, progesterone—$C_{21}H_{30}O_2$ has been isolated. Several additional oestrogenic principles have been reported, some, for example, from the urine of mares: equilin—$C_{18}H_{20}O_2$, and equilenin—$C_{18}H_{18}O_2$ (Girard, 1933).

All the sex principles possess a cyclopen taphenanthrene four-ring structure (Marrian and Haslewood, 1932) and are strikingly similar as to degree of oxidation and unsaturation.

Oestrone (theelin of Doisy) is an unsaturated hydroxyketone. Oestriol (theelol) is a trihydroxy compound, discovered by Marrian shortly after Allen and Doisy's announcement of theelin. Both these products are recoverable from urine. Butenandt and Hildebrandt demonstrated that oestriol can be converted into oestrone by dehydration *in vacuo* with potassium bisulfate.

Schwenk and Hildebrandt then reported an extremely important finding in the discovery of a dihydro derivative of oestrone —oestradiol, obtained through reduction of the ketone group to a secondary alcohol, the point of interest being that this compound is six times more potent than the oestrone from which it is derived. More striking still, this substance was soon isolated from liquor folliculi, the follicular fluid of the normal ovary by MacCorquodale *et alii* in Doisy's laboratory. There is reason to believe that it represents the pure female sex hormone, or "mother hormone," of which oestrone and oestriol are oxidation products.

Collip, in 1930 discovered an additional oestrogenic compound, recovered from urine of pregnancy. It was soon obtained in crystalline form and, regarded by Collip as a placental hormone, was given the name "emmenin," an ester of oestriol. It is of interest further to note that Andrew and Fenger have recently reported isolation of a crystalline nitrogenous compound from ovarian tissue, which is unique in that it apparently produces a delayed but prolonged oestrus in test animals, and, moreover, in that it appears to be much more powerful that oestrone. More work is needed, however, to establish clearly its separate identity.

Collip's emmenin is effective when administered orally, whereas other sex hormones are efficacious only upon injection—unless tremendous quantities are administered. Fed to immature female rats, it readily induces a condition of oestrus, without evoking any ovarian changes. It is practically ineffective in

adult rats, normal or castrate, differing sharply from the other oestrogenic compounds in this respect. Marrian and his co-workers have established emmenin as oestriol glycuronate moreover it was demonstrated that during pregnancy practically all—99%—of oestrogenic material is excreted in this form or in similar combination. Physiologically much less active than oestrone, the opinion has been advanced that the formation of oestriol, followed by the formation of its glycuronate, constitute a protective mechanism against an over-activity of oestrone and oestradiol during the course of gestation.

Finally, progesterone, an unsaturated diketone, isolated in crystalline form, as mentioned, by Allen and Corner, Fels and Slotta. Its chemical nature was established beyond further doubt by the conversion of pregnandiol (*vide supra*) and of stigmasterol, a plant sterol—specifically the wax from soy beans—into the active substance.

Is there any significance to the fact that the sex hormones appear closely related to the sterols? This seems highly probable, when we consider that the latter group of compounds are regarded as vitally important constituents of living matter. The apparent relationship is highly suggestive, although our knowledge here begin to transgress the borderline of speculation, and further work is necessary. The probable significance has been suggested by Riddle, however, in the statement that "The artificial preparation of these sex hormones from sterols suggests that *in vivo* they are intermediary metabolites or derivatives of sterols. Certain differentiated cells in the ovary (and testis as well) perhaps also placenta, apparently have the power to make these conversions. In the female, oestrone and oestriol appear to be oxidation products of the hormone actually produced by the ovary."

IV. GONADOMIMETIC ACTIVITY OF THE PLACENTA

The placenta is primarily a structure developed during pregnancy for the nourishment and respiratory exchange of the embryo. In recent years, in addition to this long-known function, sporadic evidence has appeared which has been interpreted by some investigators to indicate an actual mechanism of internal secretion. It becomes difficult, indeed, to explain certain observations on any other basis. Certainly, at least, the placenta is definitely concerned in hormonal interrelations. Without going into detail, it should be noted that Halban

(1905) pointed out that, from a clinical standpoint, the placenta must serve an endocrine function. It has since been reported that in the human being the production of ovarian hormones continues unabated following oophorectomy—the source in this circumstance having been ascribed to placental tissue (Waldstein, 1929; Probstner, 1931). Moreover, Allen and Doisy, in their search for the distribution of oestrin, found especially large quantities in the human placenta—the amount increasing progressively with the course of pregnancy. Collip, as mentioned above, has isolated a substance, emmenin, from pregnancy urine which he regards as placental in origin.

Evidence with respect to progestin elaboration by placental tissue still is uncertain. Adler, de Fremery and Tausk (1934) reported finding detectable quantities of progestin in the human placenta at term—although whether this means that it is elaborated there, or merely is retained has not been ascertained. Selye, Collip and Thomson (1935) are of the opinion that secretion of progestin occurs, since the rat uterus will show well-defined progestational changes, and the mammary glands will be maintained in a well developed condition for periods up to six days following upon ablation of the ovaries and embryos. We have obtained evidence, moreover, indicative of the role played by the placenta in maintaining hormonal balance during gestation—evidence which may be interpreted in support of the progestin-secreting concept.

It is well known, for example, that removal of the ovaries during pregnancy, at least in the more common laboratory animals, will bring gestation to an abrupt end (e. g., dog, rabbit, mouse, rat, opossum). The rule is not an invariable one, however, since it was reported some time ago that the guinea pig will frequently carry to term in the absence of ovarian tissue (Herrick; Nelson). Oophorectomy in the mare, moreover, appears to exercise no adverse effect upon the course of gestation (Cole) and, finally, the human being furnishes probably the most striking exception of all, since ablation of the gonads even in very early pregnancy may exercise no deleterious influence (Pratt; Waldstein *et al*).

In these exceptions, however, either the pregnancies are in species characteristically monotocous, i. e., in which only one fetus is carried, or the litter size is frequently limited. In the guinea pig, as an example of the latter class, the number of young ranges from one to four, and scrutiny of data reveals that

successful pregnancies after oophorectomy have been confined to animals carrying litters of not more than two. It would seem, *a priori*, that litter size may have some relation to the relative dependence upon ovarian support throughout pregnancy. When put to experimental test in the rat, this concept is borne out.

Rats commonly carry litters ranging from five to ten and twelve in number. If, however, the number of young is reduced by surgical intervention to a single fetus, removal of the ovaries shortly after midpregnancy does not interrupt the course of gestation, *provided* the additional placentae, i. e., those of the

TABLE I

EFFECT OF PLACENTAL RETENTION FOLLOWING LITTER-SIZE REDUCTION AND OOPHORECTOMY

RAT	Laparotomy*	Oophorectomy	Result
1	13†	15	23; live fetus, 5.5 gm.; 4 extra placentae.
2	14	16	23; live fetus, 5.1 gm.; 3 extra placentae.
3	13	15	22; live fetus, 4.7 gm.; 3 extra placentae.
4	12	14	24; live fetus, 5.0 gm.; not viable; 2 extra placentae.
5	13	15	23; live fetus, 4.9 gm.; 4 extra placentae.
6	13	15	23; live fetus, 5.1 gm.; not viable; 3 placentae.
7	13	15	22; live fetus, 5.0 gm.; 3 extra placentae.
8	12	14	23; live fetus, not viable; 5 extra placentae, 3 of which were detached.
9	13	16	23; fetus, 4.8 gm. alive, but died shortly after removal; 3 extra placentae.
10	13	15	23; live fetus, 4.8 gm.; 4 extra placentae, 1 detached.

*Involving removal of one ovary and fetuses in excess of one.
†The figure in each column in this and in following tables represents the day of pregnancy when operation or sacrifice was carried out.

removed fetuses, have been allowed to remain *in situ* (Table 1). As noted in the table, in ten experimental animals, in every case the remaining fetus was carried to term, and was recovered alive after being allowed to remain *in utero* for one to two days past the expected time of parturition. Spontaneous delivery does not occur—the birth mechanism, in the rat at least, appears to be seriously impaired.

The necessity for the presence of adequate placental tissue for the continuance of gestation under these circumstances is revealed by examination of Table 2, a summary of cases, operated as in the first series, in which, however, the extra placentae were included in removal. In no case was pregnancy

continued to term. Retention of one ovary under identical conditions, however (Table 3), sufficed to maintain a successful pregnancy.

TABLE II

EFFECT OF REMOVAL OF FETUSES AND PLACENTAE, WITH OOPHORECTOMY

Rat	Laparotomy	Oophorectomy	Result
15	12	15	20; placenta *in situ*, large. No fetus.
16	12	14	20; uterus empty and involuted.
17	12	15	21; uterus empty and involuted.
18	13	15	21; uterus empty and involuted.
19	12	15	21; uterus empty and involuted.
20	14	16	20; term-sized placenta *in situ;* no fetus.
21	13	15	20; uterus empty and involuting.
22	12	15	21; uterus empty and involuted.
23	13	15	22; uterus empty and involuted.
24	12	16	Allowed to run to 24th day. No evidence of delivery. Atrophic uterus upon post-mortem.
25	13	15	22; one small placenta, unattached.

It would appear therefore that presence of the ovaries is not necessarily essential during the entire course of gestation, even in the polytocous rat, provided too many young are not being carried and provided further that adequate viable placental

TABLE III

EFFECT OF RETENTION OF ONE OVARY FOLLOWING REMOVAL OF EXCESS FETUSES AND PLACENTAE

Rat	Laparotomy	Result
31	12	Delivered one fetus 22nd day; perfectly normal.
32	12	Delivered one fetus 21st day; killed by mother.
33	13	Delivered one fetus 22nd day; fetus died following day.
34	14	Delivered one fetus 22nd day; perfectly normal.
35	15	Delivered one fetus 21st day; perfectly normal.
36	14	Delivered one dead fetus 21st day.
37	14	No delivery. Empty uterus at 23rd day autopsy.
38	14	Delivered one fetus 22nd day; perfectly normal.
41	13	Delivered one fetus 22nd day; perfectly normal.
42	15	Delivered one fetus 22nd day; killed by mother.

tissue is present. The question of paramount importance is that of how the placental tissue functions in maintaining pregnancy. We do not know the answer to that as yet, since there is no evidence available that the rat placenta actually secretes pro-

gestin. The working hypothesis has been advanced that a progestin-secreting mechanism most satisfactorily explains the observations noted, but this is as yet only a hypothesis. In all events it is quite evident that the placenta serves as an adjunct to the ovaries as an endocrine mechanism—or is concerned in maintaining a proper endocrine balance. Its capacity in this respect is in all probability better developed in some species than in others—in the mare or the human being, for example, in which the corpus luteum regresses or becomes non-functional at a relatively early age and in which, presumably, the placenta can assume the functional attributes of ovarian tissue in regulating endocrine balance.

The concept of the placenta as an auxiliary gland, capable of secreting progestin, or a progestin-like principle, during pregnancy would serve to explain the curious fact that oophorectomy in some forms need not terminate pregnancy, and at the same time would not be at variance with our concept concerning the importance of the luteal hormone during pregnancy. Further work is indicated, however, before we can speak with certainty.

In conclusion, an attempt has been made in this very brief sketch to indicate the major functions of the female sex hormones. A brief survey of their discovery has been sketched, including the highlights of the final triumph of their purification, chemical elucidation and synthesis. Evidence pointing to the placenta as a possible auxiliary organ of internal secretion has been touched upon, and, although conclusive evidence awaits further experimentation, the role of the placenta in maintaining hormonal balance is such as to justify, in the writer's opinion, use of the term "gonadomimetic" with reference to its endocrine activities.

LITERATURE

Adler, de Fremery and Tausk. 1934. Nature, CXXXIII, 293.
Allen and Doisy. 1927. Physiol. Rev., VII, 600.
Ancel and Bouin. 1910. J. de Physiol. et de Path. gen., XII, 1.
Andrew and Fenger. 1936. Endocrinol., XX, 563.
Bouin and Ancel. 1909. Compt. Rend. Soc. de Biol., LXVI, 505.
Butenandt. 1929. Naturwissen., XVII, 878.
———. Deut. Med. Wochen., LV, 2171.
Collip. 1930. Canad. Med. Assn. Journ., XXII, 212, 215, 761.
———. 1932. Internat. Clin., IV, 51.
Cohen, Marrian and Watson. 1935. Lancet, L, 674.
Cohen and Marrian. 1936. Biochem. J., XXX, 57.
Corner. 1928. Am. J. Physiol., LXXXVI, 74.
Corner and Allen. 1929. Am. J. Physiol., LXXXVIII, 326.
Doisy et alii. 1930. J. Biol. Chem., LXXXVI, 499.
Fraenkel. 1903. Arch. f. Gynak., LXVIII, 438.

Fraenkel and Cohn. 1901. Anat. Anz., XX, 21.
Frank et alii. 1925. Jour. Amer. Med. Assn., LXXXV, 510.
Girard. 1933. Bull. Soc. Chim. Biol., XV, 562.
Haterius. 1936. Am. J. Physiol., CXIV, 399.
———. Proc. Soc. Exp. Biol. and Med., XXXV, 197.
Knaeur. 1896. Arch. f. Gynak., LX, 322.
Loeb. 1907. Centralbl. f. allg. Path. u. path. Anat., XVIII, 563.
Marrian and Haslewood. 1932. Biochem. J., XXVI, 25, 1227.
Ruzicka. 1936. Nature, CXXXVII, 260.
Selye, Collip and Thomson. 1935. Endocrinol., XIX, 151.
Zondek. 1928. Klin. Wochen., VII, 485.